High Induction Response Rate, but Poor Long-Term Disease Free Survival in Elderly Patients Treated Aggressively for Acute Lymphoblastic Leukemia

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Abstract

Elderly Acute Lymphoblastic Leukemia (ALL) patients are routinely offered palliative chemotherapy and best supportive care. Few studies have addressed their outcome with aggressive chemotherapy. We pursued this population based study to address the outcome of ALL patients older than 60 years treated with aggressive chemotherapy. We reviewed 32 consecutive patients treated with aggressive chemotherapy between 1989 and 2008. Twenty-seven patients (84.4%) achieved Complete Remission (CR) to induction chemotherapy of whom 23 patients (85.2%) had disease relapse. Median time to relapse was 8 (3.7-44) months. Median disease free survival and overall survival were 10.4 (0-43.9) and 16.3 (1.3-59) months, respectively. Cause of death was disease progression in 25/27 (92.6%). Seven patients (21.8%) had Philadelphia chromosome positive (Ph+) disease. Six out of these seven patients received combination chemotherapy with a tyrosine kinase inhibitor. The 3-year overall survival for the whole group was 26%; 36% for Ph+ and 23% Ph- patients. Despite the high CR rate, relapse remains inevitable and most patients died secondary to relapse. Prospective randomized studies are needed to identify the role of reduced intensity stem cell transplantation or other consolidation therapy for this dreadful disease in this age group.

Keywords: Elderly; Acute lymphoblastic leukemia; Chemotherapy; BCR-ABL

Introduction

Age remains one of the most important prognostic factors in acute lymphoblastic leukemia (ALL). The older are patients with ALL, the worse is the outcome with chemotherapy. Children and adolescents with ALL enjoy long-term survival exceeding 90% with multi-agent multi-phase chemotherapy [1,2]. In contrast adults with this disease continue to have poor outcome with long-term survival rates of 40% at best [3,4]. Even in the adult group, long-term survival rates are not the same among different age subgroups. This was well demonstrated with 759 adults treated on five CALGB studies from 1988-2002. The three year over-all Survival (OS) declined from 58% for patients under age 30 to 38% for those 30-59 years old and was only 12% for those patients older than 60 years [5]. Similar results were reported from other groups with median OS of 6-11 months for the elderly group [6,7]. Despite the fact that adult ALL including elderly patients achieve a high CR rate to induction chemotherapy (70-90%), the reported 3-year OS for elderly ALL patients is only 11-12% [6,7]. This can partly be explained by biology of the disease, comorbidities, induction failure rates and treatment complications during chemotherapy.

This study represents a retrospective review focusing on elderly ALL patients who received aggressive chemotherapy to determine complete remission rate, complication after chemotherapy, relapse rate and long term outcome. Another aspect of this review was to determine the outcome with tyrosine kinase inhibitors in Ph+ elderly ALL compared to Ph- patients.

Materials and Methods

This is a retrospective analysis of all patients with confirmed diagnosis of ALL who were 60 years or older, referred and received aggressive IV chemotherapy at the Leukemia/ BMT program of BC, Vancouver, Canada between December1989 and February 2008. These patients were identified through a retrospective review of our program database (BMT Serve 3.1.4, StemSoft, Vancouver Canada) followed by chart review of all cases who satisfied the above criteria. ALL diagnosis was confirmed by bone marrow aspiration, biopsy and flow cytometry. Metaphase cytogenetics was performed on diagnostic marrow samples. Ph-positivity was confirmed by conventional cytogenetics, FISH or molecular studies (PCR for bcr/abl).

This study was approved by the University of British Columbia/BC Cancer Agency Research Ethics Board as part of a broad retrospective analysis of clinical characteristics and outcomes of all ALL patients treated at the L/BMT Program of BC. All patients included received a consistent induction /consolidation and maintenance chemotherapy as per our in house modified protocol. Phase I induction chemotherapy consisted of daunorubicin (30-60 mg/m² IV) daily for 3 days, vincristine (1.4 mg/m² IV, max 2 mg) weekly for 3-4 weeks and prednisone (30-60 mg/m² PO) daily for 20-28 days. L-asparaginase was omitted for all patients due to age. Phase II induction consisted of cyclophosphamide (650 mg/m² IV) repeated once after 14 days, cytarabine (75 mg/m² IV), daily on days 1-4 and 8-11 and mercaptopurine (60 mg/m² PO) daily for 14-28 days. Consolidation chemotherapy consisted of 1-2 cycles of cytarabine (75 mg/m² IV) and tenoposide (60 mg/m² IV) both were given daily for 5 consecutive days. Modified intensification was given in selected patients according to performance status, comorbidities and previous chemotherapy

toxicity. It consisted of vincristine (1.5 mg/m^2 IV, max 2 mg) once weekly for 3-4 weeks, daunorubicin (25 mg/m^2 IV) once weekly for 3 weeks, Decadron (10 mg/m^2 PO) daily for 10-14 days, cyclophosphamide (650 mg/m^2 IV) once only. Methotrexate (20 mg/m^2 PO) once weekly and mercaptopurine (75 mg/ m^2 PO) daily were given for a total of 2.5 years as a maintenance therapy for selected patients. Ph positive patients also received tyrosine kinase inhibitor (Imatinib mesylate at a dose of 400-600 mg daily until disease progression/relapse) as a part of treatment protocol either during induction, consolidation or at relapse.

Statistical methods and definitions

Complete remission was defined as the reduction of BM blasts to less than 5% with recovery of peripheral blood counts. Relapse was defined as the reappearance of blast cells in peripheral blood or/and more than 5% of blast cells in bone marrow. Overall survival was measured from the date of diagnosis until death from any cause for all patients. Patients who are still alive were censored at the last follow up date. Disease free survival was measured from the date of achieving complete remission to the date of relapse or death and patients who are alive were censored at the last follow up date. OS, DFS were estimated using Kaplan-Meier method. Univariate analysis of the differences in DFS and OS were conducted with log-rank tests.

Results

Patient characteristics

Between December 1989 and February 2008, Thirty two patients (8.7 % of all referred adult ALL patients) were elderly ALL who received intensive IV chemotherapy, median age was 66.0 years (range 60.1-76.1), half of them were females. All had ECOG performance status ≤ 2, median white blood cell count at diagnosis was 7.4 ×10^9/L (range 0.8-43). Twenty nine patients had B cell phenotype; two had T cell and one with no flow cytometry result available. Thirteen patients had myeloid antigen co-expression. Only one patient had CNS involvement by CSF cytology at diagnosis (Table 1). None of the 32 patients had a mediastinal mass by chest-x ray. Seven patients (28%) were Ph+. Six patients were hyperdiploid (>46 chromosomes) and four patients hypodiploid (<45 chromosomes). One patient had 11q23 abnormality (Table 2).

	Ph+ group	Ph- group	All
	N=7	N=25	N=32
Sex, Male/Female	05-Feb	Nov-14	16/16
Median age, year, (range)	68.6 (62.3-76.1)	65.4 (60.1-74)	66.0 (60.1-76.1)
Median white blood cell count, x109/L, (range)	11 (6.3-38.7)	4.3 (0.8-43)	7.4 (0.8-4.3)
Immunophenotype, B- cell/T- cell	7/0	22-Feb	29/2
ECOG performance status 0-1/2	05-Feb	15-Oct	20-Dec

Table 1: Patient characteristics

Outcomes

All patients received induction treatment consisting of daunorubicin, vincristine and prednisone as outlined before. CR was achieved in 84.4% (27/32). The CR rate was not different between Ph+ and Ph- patients (Table 3). Phase two induction was given in 66.7% (18/27) of patient who were in remission. Consolidation chemotherapy was given in 62.9% (17/27) which was 1-2 cycles of cytarabine and tenoposide. Six patients also received modified intensification chemotherapy with vincristine, daunorubicin, and cyclophosphamide. Maintenance oral methotrexate and mercaptopurine was given in 20 patients that included 4 patients who did not receive consolidation chemotherapy.

Remission was achieved in 84.4%, but was short lived with Relapse Rate (RR) of 85.2% (23/27) of patient who achieved CR. Median time of relapse from diagnosis was 240 days (range112-1317). Thirteen relapsed patients in the Ph- group received re-induction chemotherapy. Only 4 patients (30%) went into second CR but all of them had a second relapse and died secondary to disease progression. In the Ph+ group, all patients who achieved remission had relapse. Four patients had a tyrosine kinase inhibitor after relapse. Three patients (75%) achieved a second CR. Two patients were still alive at last follow up after 31months and 26 months from diagnosis; one of whom achieved a second complete molecular response by quantitative PCR with Dasatinib 40 mg daily.

Median DFS and OS were 313 days (range 0-1317) and 489 days (range 38-1770), respectively. The 3-year OS for the whole group was 26%; 36% for Ph+ and 23% for Ph- patients (Table 3). The major cause of death was disease progression in 92.6 % (25 patients). One patient died secondary to lung cancer and another died from progressive fungal infection. Both patients died in first CR.

In term of toxicity to induction chemotherapy, 23 patients developed febrile neutropenia with positive blood cultures in six patients. Two patients developed septic shock. Three patients had fungal infection proceeding induction therapy. For non-infectious complication, seven patients developed symptomatic neuropathy. Five patients developed cardiac complications including atrial fibrillation (2), heart failure (2) and unstable angina (1); all improved and stabilized with conservative medical therapy. Two patients developed reversible confusion state. One patient also developed pleural effusion. There were no toxic deaths related to chemotherapy.

Cytogenetics	Number of patients
Philadelphia chromosome positive	7

Hyperdiploid	6
Hypodiploid	4
Normal	8
Others failed=3, t(4,11) = 1, del(5) =1, i(22)=1, 11q23 abnormality = 1	7

Table 2: Cytogenetics

	All Patient	Ph+ group	Ph- group	P value
Number	32	7	25	
CR	84.40%	85.70%	84%	NS
3-year DFS	15%	0%	19%	NS
3-year OS	26%	36%	23%	NS

Table 3: Complete remission rate and 3-year disease free and overall survival

Effect of Tyrosine kinase inhibitors in combination treatment for Philadelphia chromosome positive elderly ALL

Six out of the 7 patients who had Ph+ ALL received combination chemotherapy with a tyrosine kinase inhibitor as a part of protocol. Four patients received Imatinib mesylate as part of the consolidation therapy of whom two patients received Dasatinib in the relapse setting. Another two patients were not exposed to TKI during induction/consolidation and received Imatinib mesylate in the relapse setting. Taking into consideration the small numbers of Ph + patients and the fact that they did not receive TKI therapy in a homogenous protocol, it is difficult to withdraw any conclusion to evaluate TKI benefit in this study. OS in the Ph+ patients was 36% at 3 years compared to 23% in Ph- patients. Two Ph+ patients were still alive at last follow up with one of them achieving complete molecular response by quantitative PCR on on going tyrosine kinase inhibitor.
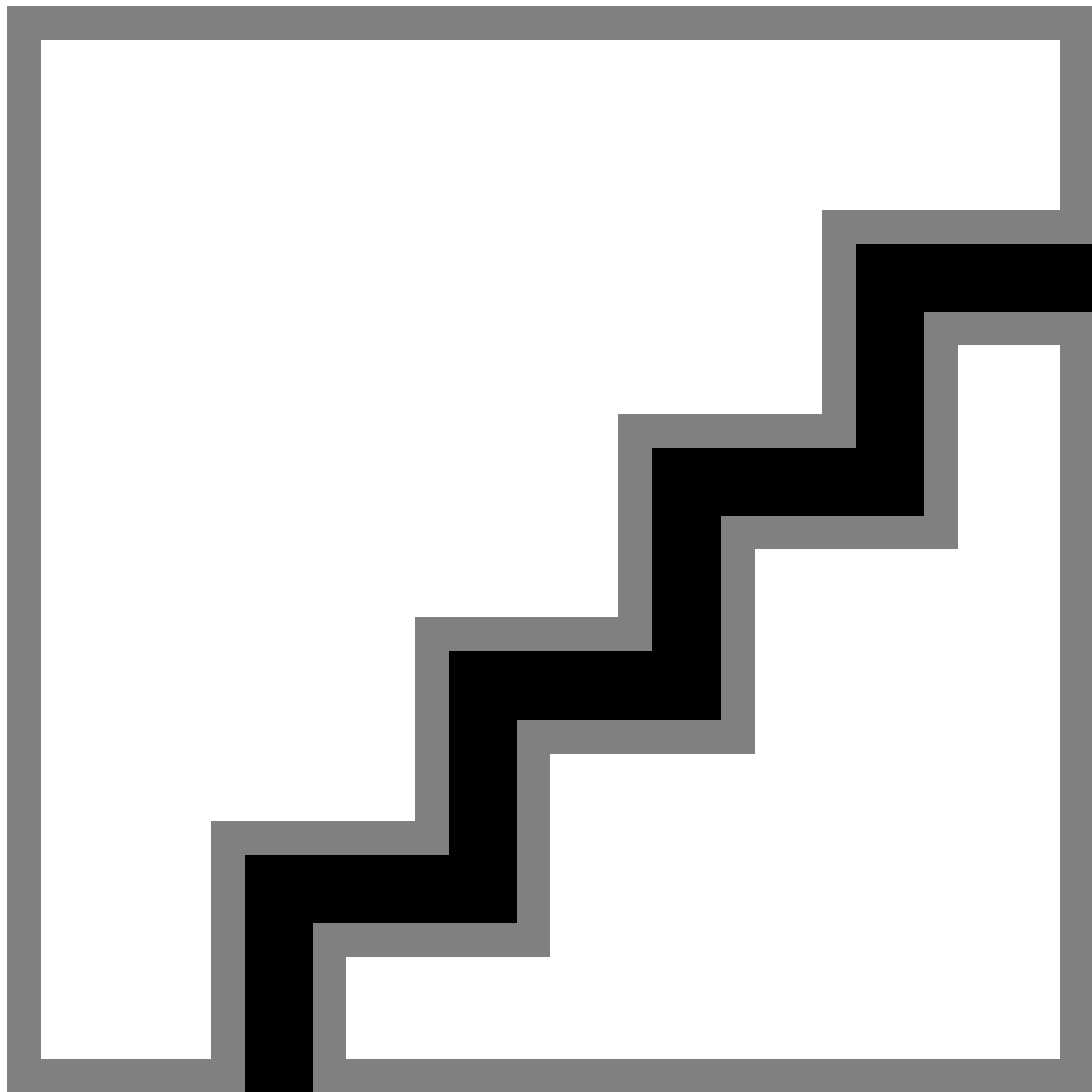
Figure 1: Overall survival, Disease free survival, Disease free survival by cytogenetics, Overall survival by cytogenetics

Discussion

Acute leukemias in the elderly, in general, and elderly ALL, in particular, have received little attention from researchers/literature. ALL in the elderly (aged 60 years and over) is a rare disease with a reported annual incidence of 0.9 to 1.6 cases per 100,000 (6); it accounts for 18-31% of all adult ALL [5,6]. As the size of the elderly population continues to increase, health care professionals can expect to see a steadily growing number of elderly patients with cancer including ALL [8].

This retrospective observational study is one of few describing the outcome of intensive chemotherapy in a carefully selected group of elderly ALL patients. In addition to the description of biologic features and outcomes, it also might serve as a background for any potential future prospective trial in this age group.

The percentage of elderly ALL referred and treated in this study, as a proportion of all ALL patients, was significantly lower than that reported in the literature (8.7% vs. 31% respectively) [9]. This clearly reflects a selection bias in terms of referral. All patients in this study who were referred to us and received chemotherapy were carefully selected elderly ALL patients with good performance status. They were referred, to start with, because they were fit and considered good candidates for intensive chemotherapy. Patients with significant comorbidities were either not referred to us or when referred did not receive aggressive treatment and therefore were excluded from this

cohort. The median age of elderly ALL in this report is 66 years which is quite comparable to that reported in the literature [6,10,11].

Over the past three decades, survival of ALL patients has improved in all age groups, but not in the elderly age group [12]. The CR rate reported in literature for this group varies from 32% to 73% with high reported induction Treatment Related Mortality (TRM), 15-36% [7,9-15]. Despite relatively good initial response to induction chemotherapy, Relapse Rate (RR) remains high and most patients succumb to their disease. This discrepancy in outcome between children, young adults, adults and elderly ALL patients is due to age-related factors, such as comorbidities, functional, social, and cognitive impairment that complicate the management of older patients. Differences in biology of the disease, immunophenotype and cytogenetics in elderly ALL also play an important role. Elderly ALL patients have higher rate of secondary ALL due to previous malignant diseases/therapy compared to younger groups [6]. Elderly ALL patients also have higher incidence of B-cell phenotype and lower T-cell phenotype, higher CD34 expression and co-expression of myeloid markers on lymphoid blast cells compared to younger patients [5,6,16]. This study confirmed the above findings where B cell ALL constituted 90% of patients in this report.

Our single institution experience in treating elderly ALL with modified intensive chemotherapy showed that despite the reasonable high CR rates (84.4%), the overall survival of these patients remained poor with a median survival of a few months. The treatment associated mortality in our study group was unexpectedly low. This is clearly related to the highly selective approach in offering intensive chemotherapy for only fit patients. Toxicity secondary to intensive chemotherapy is of major concern for elderly patients; this is due to co-morbidities, poor nutritional status, interaction between various medications and differences in pharmacokinetic and pharmacodynamic profile. The PETHEMA group reported early death in 36.4% of Ph negative elderly ALL patients after receiving induction chemotherapy [11]. The induction chemotherapy used in our cohort is less intense compared to the PETHEMA report. Treatment related toxicity and side effects in our cohort were mainly febrile neutropenia seen in 72% which resolved after receiving antibiotics and with count recovery. Non-infectious complications included cardiac and neurological; those also were reversible.

Unfortunately in this small cohort, we were unable to identify a subset of ALL patients older than 60 years of age who gained more benefit from intensive chemotherapy than others.

Karyotype is an independent prognostic factor in adult ALL. It has shaped our current classification system and is used to direct therapy [17]. It is not entirely clear whether it retains its significance in this age group. The t(9;22) is the most prevalent chromosomal abnormality in adult ALL and is present in 11-30% of patients [6,7,9,12,16]. The incidence is strongly correlated with age, rising from 6% in adolescents (less than 25 years old) to 14% for those 25-35 years old, 33% for those 36–55 years old, and 53% for patients older than 56 years [5,18]. In our study, the incidence of Ph+ was 28% which is comparable to that reported by the CALGB group (33%) [19].

The variation in overall incidence is probably due to differences in the age distribution of patient cohorts. Translocation (4;11) dictates poor outcome and strongly correlates with age [17]. On the contrary, ETV6/RUNX1 fusion and hyperdiploidy are good risk karyotypes that are common in childhood ALL, but found only in 10% of adult ALL [20].

Relapse remains the major problem for this age group with a RR in our study of 85.2%. The outcome of relapse in adult ALL patients in general is disappointing and it is even worse in this age group. The second CR for Philadelphia negative group after reinduction chemotherapy was only 30%, but was short lasting and second relapse followed. Disease progression was the major cause of death. The median EFS and OS was only 10.4 and 16.3 month for the whole group. Other groups also reported similar disappointing long term outcomes, with median EFS and OS of only 6-8.3 months and 5-7 months, respectively [6,13].

The outcome of intensive chemotherapy in elderly ALL is dismal, but compared favorably to patients receiving only palliative supportive therapy. Pagona et al. reported a non-randomized trial comparing patients treated with intensive chemotherapy and others with palliative supportive care. The later group had shorter median OS 2.6 months compared to 15 months in the other group. The intensive chemotherapy group required longer duration of hospitalizations [9]. A recent study from Toronto by Martell et al, reported their outcome after using a modified pediatric-based protocol, the CR rate was 75% median OS of nearly 3 years and a 40% 5-year OS, but their induction TRM was still high at 20% [21].

The CR rate from intensive chemotherapy in elderly ALL patients is impressively high, but relapse remains inevitable with chemotherapy alone. This fact provides the rationale of using other modes of consolidation therapy such as bone marrow transplantation after reduced intensity conditioning chemotherapy which might play a positive role in consolidating/prolonging CR. Transplantation is the most potent known antileukemic therapy and might reduce the risk of relapse and prolong survival in elderly ALL.

Bone marrow transplantation may have limitations in this population due to age, organ dysfunction, performance status and co-morbidities. Recently reduced intensity type of bone marrow transplantation is playing a significant role and is offered for wider range of patients including those above the age of 65 years. Stein et al in a small retrospective analysis reported the outcome of transplant after Reduced Intensity Conditioning regimen (RIC) for high risk ALL including elderly ALL. This study included a mixture of ALL patients, aged 50 years or older (42%), patients with compromised organ function and patients who had prior transplantation. The long term outcome was impressive with OS and DFS at 2 years of 61.5%. In this study, 86% of patients developed chronic Graft Versus Host Disease (GVHD) which suggests that graft versus leukemia effect still plays a major role in preventing relapse in this group [22].

Another retrospective study by the EBMT group also confirmed the significance of GVHD in ALL patients. Ninety-seven adult ALL patients underwent RIC allogeneic stem cell transplantation. With a median follow-up of 2.8 years, 2 year overall-survival and leukemia-free survival for patients in first complete remission were $52 \pm 9\%$ and $42 \pm 10\%$, respectively. Chronic GVHD was the most significant factor associated with improved overall-survival [23].

Philadelphia chromosome is known as a significant adverse factor in ALL. Prior to the introduction of Tyrosine Kinase Inhibitors (TKI), Ph positive ALL patients had a lower CR rate compared with the Ph negative group and short long term survival of less than 10% when treated with chemotherapy alone [24,25]. Stem cell transplantation has been the standard of care and the only curative option for this group with long term overall survival around 27-65% [26,27]. All patients in this group had relapse after induction treatment. TKI was successful in

attaining second remissions after relapse in this population. Three patients out of four (75%) achieved a second complete remission post second line TKI compared to 30% after chemotherapy in non-Philadelphia chromosome patients. Two Ph + patients were still alive at last follow up; one of whom achieved a complete molecular response by quantitative PCR with a second generation TKI.

The Italian group showed interesting results in elderly Ph positive ALL patients who received induction treatment with high dose imatinib and steroids. The hematologic response rate was 100%. During induction, 13 patients (45%) developed non-hematologic toxicity (more than grade 2 by the WHO criteria) which resolved after temporary discontinuation of treatment. No induction deaths were reported. The probability of OS and DFS at 12 months was 74% and 48%, respectively [27].

Ottman et al., in a small prospective randomized trial compared the outcome between induction with imatinib and multi agent chemotherapy in 55 Ph positive elderly ALL patients. Result confirmed that induction with imatinib had a higher CR rate of 96.3% compared with 50% with chemotherapy. The serious adverse events were lower in imatinib group; 39% vs. 86%. In this study, the group that received chemotherapy as an induction still gained benefit by receiving imatinib for reinduction, consolidation, and maintenance. The difference in OS was not statistically significant between the two groups [28].

We acknowledge that our cohort included small number of patients that were treated over a long period of time. Over the past 20 years there has been significant improvement and advances in supportive care and management of infectious complications. This might be reflected as improvement in outcome in this age group.

In conclusion, our study confirms that even a properly highly selected group of elderly ALL with good PS, treated with intensive chemotherapy still have poor long term OS. Despite achieving high CR and low TRM rate with intensive chemotherapy, RR remains high and most patients die secondary to disease progression. The role of novel agents or RIC allogeneic transplantation should be explored and may play a future role in consolidating remission and prolonging survival in this age group. Tyrosine kinase inhibitors when used in Ph+ elderly ALL improve their outcome compared to Ph- counterparts.

Acknowledgement

References

1. Gaynon PS, Angiolillo AL, Carroll WL, Nachman JB, Trigg ME, et al. (2010) Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: a Children's Oncology Group Report. Leukemia 24: 285-297.

2. Pui CH, Pei D, Sandlund JT, Ribeiro RC, Rubnitz JE, et al. (2010) Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. Leukemia 24: 371-382.

3. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, et al. (2005) Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 106: 3760-3767.

4. Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, et al. (2004) Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol 22: 4075-4086.

5. Larson RA (2005) Acute lymphoblastic leukemia: older patients and newer drugs. Hematology Am Soc Hematol Educ Program .

6. Thomas X, Olteanu N, Charrin C, Lhéritier V, Magaud JP, et al. (2001) Acute lymphoblastic leukemia in the elderly: The Edouard Herriot Hospital experience. Am J Hematol 67: 73-83.

7. Taylor PR, Reid MM, Proctor SJ (1994) Acute lymphoblastic leukaemia in the elderly. Leuk Lymphoma 13: 373-380.

8. Edwards BK, Howe HL, Ries LA, Thun MJ, Rosenberg HM, et al. (2002) Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. Cancer 94: 2766-2792.

9. Pagano L, Mele L, Casorelli I, Fianchi L, Di Febo A, et al. (2000) Acute lymphoblastic leukemia in the elderly. A twelve-year retrospective, single center study. Haematologica 85: 1327-1329.

10. Taylor PR, Reid MM, Bown N, Hamilton PJ, Proctor SJ (1992) Acute lymphoblastic leukemia in patients aged 60 years and over: a population-based study of incidence and outcome. Blood 80: 1813-1817.

11. Sancho JM, Ribera JM, Xicoy B, Morgades M, Oriol A, et al. (2007) Results of the PETHEMA ALL-96 trial in elderly patients with Philadelphia chromosome-negative acute lymphoblastic leukemia. Eur J Haematol 78: 102-110.

12. Pulte D, Gondos A, Brenner H (2009) Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. Blood 113: 1408-1411.

13. Robak T (2004) Acute lymphoblastic leukaemia in elderly patients: biological characteristics and therapeutic approaches. Drugs Aging 21: 779-791.

14. Offidani M, Corvatta L, Centurioni R, Leoni F, Malerba L, et al. (2003) High-dose daunorubicin as liposomal compound (Daunoxome) in elderly patients with acute lymphoblastic leukemia. Hematol J 4: 47-53.

15. Brandwein JM, Gupta V, Wells RA, Schuh AC, Schimmer AD, et al. (2005) Treatment of elderly patients with acute lymphoblastic leukemia--evidence for a benefit of imatinib in BCR-ABL positive patients. Leuk Res 29: 1381-1386.

16. Gokbuget N, Hoelzer D, Arnold R, Böhme A, Bartram CR, et al. (2001) Subtypes and treatment outcome in adult acute lymphoblastic leukemia less than or greater than 55 years. Hematol J.1: 186.

17. Moorman AV, Harrison CJ, Buck GA, Richard SM, Secker-walker LM, et al (2007) Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood 109: 3189-3197.

18. Appelbaum FR (2005) Impact of age on the biology of acute leukemia. American Society of Clinical Oncology Educational Book: 528-532

19. Wetzler M, Dodge RK, Mrózek K, Carroll AJ, Tantravahi R, et al. (1999) Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. Blood 93: 3983-3993.

20. Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR (2008) Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. Blood 111: 2563-2572.

21. Martell MP, Atenafu EG, Minden MD, Schuh AC, Yee KW, et al. (2013) Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. Br J Haematol 163: 458-464.

22. Stein AS, Palmer JM, O'Donnell MR, Kogut NM, Spielberger RT, et al (2009) Reduced-intensity conditioning followed by peripheral blood stem cell transplantation for adult patients with high-risk acute lymphoblastic leukemia. Biol Blood Marrow Transplant 15: 1407-14.

23. Mohty M, Labopin M, Tabrizzi R, Theorin N, Axel A Fauser AA, et al (2008) Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a

retrospective study from the European Group for Blood and Marrow Transplantation. Haematologica 93: 303-6.

24. Ottmann OG, Wassmann B (2005) Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program .

25. Houot R, Tavernier E, Le QH, Lhéritier V, Thiebaut A, et al (2004) Philadelphia chromosome-positive acute lymphoblastic leukemia in the elderly: prognostic factors and treatment outcome. Hematology 9: 369-376

26. Avivi I, Goldstone AH (2003) Bone marrow transplant in Ph+ ALL patients. Bone Marrow Transplant 31: 623-632.

27. Vignetti M, Fazi P, Cimino G, Martinelli G, Di Raimondo F, et al (2007) Imatinib plus steroids induce complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 109: 3676-3678.

28. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, et al. (2007) Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer 109: 2068-2076.